Exogenous leukemia inhibitory factor stimulates oligodendrocyte progenitor cell proliferation and enhances hippocampal remyelination.

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Public Summary:
Oligodendrocytes are critical cells of the central nervous system that coat the long axons of neurons in myelin, which serves to both increase the rate of communication between neurons and to provide support to the axons, keeping them healthy. In multiple sclerosis (MS), inflammation-associated oligodendrocyte loss results in brain, spinal cord, and optic nerve lesions where axons are stripped of their myelin. Together the inflammation, demyelination, and ensuing damage to axons cause the motor, vision, and cognitive dysfunctions that characterize the disease. Current therapies aimed at suppressing or altering the inflammatory response reduce the frequency of relapses, but these therapies do not prevent disease progression, and are largely ineffective in later stages of the disease. Therefore, additional therapeutic approaches are necessary. We are investigating the therapeutic potential of the cytokine LIF for MS. In the nervous system, LIF is an injury-induced cytokine that has been previously shown to promote the survival of oligodendrocytes in an animal model of MS and to enhance the survival of motor neurons after their axons have been severed. In addition we previously showed that LIF expands the pool of neural stem cells available for repair. In this report we show that delivering LIF, using a viral gene therapy vector, to the central nervous system promotes repair following oligodendrocyte loss and demyelination by stimulating the generation of new myelinating oligodendrocytes from stem and progenitor cells distributed throughout the central nervous system. This new finding together with other known functions of LIF suggest that LIF has multiple activities that make it an attractive therapeutic candidate for MS.

Scientific Abstract:
New CNS neurons and glia are generated throughout adulthood from endogenous neural stem and progenitor cells. These progenitors can respond to injury, but their ability to proliferate, migrate, differentiate, and survive is usually insufficient to replace lost cells and restore normal function. Potentiating the progenitor response with exogenous factors is an attractive strategy for the treatment of nervous system injuries and neurodegenerative and demyelinating disorders. Previously, we reported that delivery of leukemia inhibitory factor (LIF) to the CNS stimulates the self-renewal of neural stem cells and the proliferation of parenchymal glial progenitors. Here we identify these parenchymal glia as oligodendrocyte (OL) progenitor cells (OPCs) and show that LIF delivery stimulates their proliferation through the activation of gp130 receptor signaling within these cells. Importantly, this effect of LIF on OPC proliferation can be harnessed to enhance the generation of OLs that express myelin proteins and reform nodes of Ranvier in the context of chronic demyelination in the adult mouse hippocampus. Our findings, considered together with the known beneficial effects of LIF on OL and neuron survival, suggest that LIF has both reparative and protective activities that make it a promising potential therapy for CNS demyelinating disorders and injuries.